I. Remarks

Claims 1-21 and 23-25 are currently pending. Claims 1-6, 12-21, and 23-24 stand withdrawn pursuant to a Restriction Requirement. Claims 7-11 and 25 are under examination on their merits.

Claim 7 has been amended with this response. This amendment does not add new matter and its entry is requested.

II. Claim rejections under 35 U.S.C. § 112

Claims 7-11 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as their invention. Applicants respectfully traverse.

A) With respect to claim 7, the Office has concluded that the recitation of "the leucine zipper domain" in claim 7, part (i) allegedly does not have antecedent basis in the claim. Applicants have amended claim 7 as suggested by the Office which renders this rejection moot. Withdrawal is therefore requested.

B) With respect to claim 11, the Office has also concluded that claim 11 is allegedly ambiguous and unclear. In particular, the Office alleges that there is an insufficient nexus between part (i) and (ii) of said claim because they read on separate components in a solution. Applicants respectfully traverse.

Insofar as Applicants understand the instant rejection, claim 11 properly does read upon separate polynucleotide components in a solution. The polynucleotide molecules can be present on the same or on separate expression vector molecules as long as both polynucleotides are expressed at the same time. Support for this reading is found in the instant specification at page 43, line 30 - page 44, 12. Therefore, Applicants assert that the meaning of the recitation "recombinant system" is clear and definite when evaluated in light of the instant specification. As such, withdrawal of this rejection is respectfully requested.

III. Claim rejections under 35 U.S.C. § 103(a)

Claims 7-11 and 25 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 6,309,645 to Rhode et al. (the '645 patent) in view of U.S. Patent No. 5,932,448 to Tso et al. (the '448 patent). Specifically, the Office has concluded the instantly claimed fusion polypeptides are prima facie obvious because one of ordinary skill in the art would have been motivated

to substitute the IgG-derived dimerization domain taught by the '645 patent with a leucine zipper dimerization domain taught by the '448 patent to arrive at the claimed T cell antigen presenting domain-leucine zipper domain fusion protein. Applicants respectfully traverse.

Claims 7-11 and 25 are not obvious in view of the prior art cited by the Office. The establishment of a prima facie case of obviousness requires, in part, a suggestion or motivation to modify the prior art references (MPEP 2143). Applicants assert that the Office has failed to provided an objective, supported motivation to combine the cited prior art. The cited references actually teach the skilled artisan away from the proposed combination, demonstrating that the Office has impermissibly used the instant application as a blueprint to construct the obviousness rejection.

Furthermore, Applicants assert that the prior art modifications suggested as obvious by the Office alter the principles of operation of the prior art. If the proposed modifications or combination of the prior art would change the principle of operation of the prior art invention being modified, the teachings of the references are thus not sufficient to render the claims prima facie obvious (MPEP 2143.01). Therefore, no prima facie case of obviousness has been or can be established with the suggested combination of prior art references.

In making the obviousness rejection, the Office concludes that the skilled artisan would have been motivated to modify the MHC- IgG fusion construct taught by the '645 patent by substituting the IgG-derived dimerization domain of the construct with a leucine zipper oligomerization domain taught by the '448 patent. The Office then summarizes the teachings of each prior art reference but otherwise fails to point to or provide an objective, supported motivation for substituting an IgG-derived domain with a leucine zipper domain. Although the Office also sets forth several conclusions regarding the alleged properties of the substituted molecule, it fails to provide support for them as motivating factors.

In fact, Applicants assert that a closer reading of the '645 patent would lead the skilled artisan away from the substitution suggested by the Office. Based on the large size of the immunoglobulin molecules successfully utilized in the '645 patent and the large structures utilized by the prior art[1] in building multivalent MHC fusions, the skilled artisan would not have been motivated to use nor would have reasonably expected success in using the significantly smaller leucine zipper domain, which is only a fraction of the molecular weight of the IgG-derived domain utilized in the '645 patent.

The '645 patent teaches multivalent MHC-peptide complexes are desirable because certain T cells may only be activated by multivalent complexes. The reference identifies several desirable

multivalent MHC fusion complexes including 1) MHC molecules linked to a dimerizing immunoglobulin molecule (like IgG, IgM, or Fab'2) and 2) MHC molecules chemically cross-linked using a synthetic chemical polymer (like a dendrimer) (see '645 at column 16, lines 5-27.) A prior art reference cited by the '645 patent [J, McCluskey et al. (see footnote 1; reference is enclosed herein)] uses agarose beads, dextran T-2000, or polystyrene plates to generate multivalent fusion species. The artisan of ordinary skill would recognize that these molecules are all large structures- particularly when compared to the leucine zipper utilized by the instant invention. Immunoglobulin domains are large protein complexes with molecular weights averaging from 146,000 Daltons for IgG classes to 970,000 Daltons for IgM classes[2]; the 9th generation dendrimers have a theoretical molecular weight of greater than 40,000 Daltons[3]; dextran T-2000[4] has an average molecular weight of 2,000,000 Daltons; and the cited agarose beads have an average particle size of 90 μm[5].

In constrast, the leucine zipper domains provided by the '448 patent are relatively small proteins, generally around 35 amino acids in length (see '448 at column 5, lines 1-7.) Two of the exemplary leucine zippers described in the '448 patent at Figures 1A and 1B have approximate molecular weights of 4.5 Daltons, 10-100 times lower than the immunoglobulin domains cited by the '645 patent. The leucine zipper is also structurally dissimilar from the dendrimers, agarose beads, and dextran cited in the prior art as useful molecules to generate multivalent MHC fusion molecules. The leucine zipper is a smaller peptide while the latter are all large polymeric molecules. Therefore, Applicants assert that the skilled artisan would not have been motivated to substitute in a leucine zipper for any of the large prior art molecules because it has significantly different properties from those taught.

Moreover, Applicants assert that the prior art modifications suggested as obvious by the Office alters the principles of operation of the '645 patent's construct because it drastically reduces the size and nature of the '645 construct. The substitution of a leucine zipper (comprising on average 35 amino acid residues) for the immunoglobulin-derived domain used in '645 (comprising at least 500 – 600 amino acid residues[6]) significantly reduces the size of the fusion construct. The Office has recognized that this alteration will likely result in a complex with different physical and immunological properties[7], which Applicants assert is evidences that the principle of operation of the '645 has been altered by the suggested substitution.

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[1] A prior art reference cited by the '645 patent, J, McCluskey et al., (1988), J. Immunol., 141: 14521-1455, utilizes agarose beads, 2,000,000 Dalton dextran, or polystyrene plates to construct multivalent
[2] See Ivan Roitt et al., Immunology 65-71 (Mosby 6th ed. 2001) at page 67, which is enclosed herein.
[3] See http://www.dendritech.com/pamam.html
[4] See McCluskey et al., (1988), J. Immunol., 141: 14521-1455 at page 1453, second column,
[5] These beads are identified in the Materials and Methods section as CNBr-activated Sepahrose 4B, whose average particle size is 90 μm.
[6] In the '645 patent, one of the constructs taught utilized the kappa constant domain (or light chain constant domain which is generally of a size of approximately 107 residues) and the murine IgG2b constant domain (or heavy chain constant domain which is generally of a size of approximately 450 residues.)
[7] See the Office Action mailed March 24, 2005 at page 4, final sentence prior to the Conclusion section.

Additionally, Applicants assert that it is reasonable to conclude by the teachings discussed supra that large molecules, such as the taught immunoglobulin domains or dextran polymers, are required for the operation of the '645 constructs. The '645 patent and the prior art use domains that are all very large complexes, whether proteins or polymers. Importantly, Applicants have not found a teaching or suggestion, nor has the Office provided one, that a dimerizing or oligomerizing molecule with significantly smaller molecular weight would be a functional replacement for the large, complex molecules previously utilized. Therefore, Applicants assert that the drastic reduction in size of the dimerization domain caused by the substitution of a leucine zipper for the IgG hybrid does alter the principles of operation of the '645 patent's construct.

In summary, Applicants assert that the Office has failed to provide an objective, supported motivation to combine the cited prior art but rather has impermissibly used the instant application as a blueprint to construct the obviousness rejection. Furthermore, the prior art modifications suggested by the Office alters the principles of operation of the prior art thus rendering the combination insufficient to render said claims obvious. For these reasons, Applicants respectfully request that the withdrawal be withdrawn.

IV. Conclusion

No fee is deemed necessary in connection with the filing of this communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 07-1074.

Respectfully submitted,

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